

Allergy Workup in the Diagnosis of COVID-19 Vaccines-Induced Hypersensitivity Reactions and Its Impact on Vaccination

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Keywords

COVID-19 · Vaccine · Allergy · Skin test · Polyethylene glycol · Polysorbates

Abstract

Introduction: Immediate and delayed hypersensitivity reactions (HSR) to COVID-19 vaccines are rare adverse events that need to be prevented, diagnosed, and managed in order to guarantee adherence to the vaccination campaign. The aims of our study were to stratify the risk of HSR to COVID-19 vaccines and propose alternative strategies to complete the vaccination. **Methods:** 1,640 subjects were screened for vaccinal eligibility, according to national and international recommendations. Among them, we enrolled for allergy workup 152 subjects, 43 with HSR to COVID-19 vaccines and 109 at high risk of HSR to the first dose. In vivo skin tests with drugs and/or vaccines containing PEG/polysorbates were performed in all of them, using skin prick test and, when negative, intradermal tests. In a subgroup of patients resulted negative to the in vivo skin tests, the programmed dose of COVID-19 vaccine (Pfizer/BioNTech) was administered in graded doses regimen, and detection of

neutralizing anti-spike antibodies was performed in these patients after 4 weeks from the vaccination, using the SPIA method. **Results:** Skin tests for PEG/polysorbates resulted positive in only 3% (5/152) of patients, including 2 with previous HSR to COVID-19 vaccines and 3 at high risk of HSR to the first dose. Among the 147 patients with negative skin tests, 97% (143/147) were eligible for vaccination and 87% (124/143) of them received safely the programmed COVID-19 vaccine dose. Administration of graded doses of Pfizer/BioNTech vaccine were well tolerated in 17 out of 18 patients evaluated; only 1 developed an HSR during the vaccination, less severe than the previous one, and all developed neutralizing anti-spike antibodies after 4 weeks with values comparable to those subjects who received the vaccine in unfractionated dose. **Conclusion:** On the whole, the usefulness of the skin tests for PEG/polysorbates seems limited in the diagnosis of HSR to COVID-19 vaccines. Graded doses regimen (Pfizer/BioNTech) is a safe and effective alternative strategy to complete the vaccinal course.

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Introduction

The COVID-19 is a devastating global pandemic with limited therapeutic options. In this scenario, vaccination represents the most effective global strategy to achieve optimal population herd immunity [1–4]. Since the beginning of the COVID-19 vaccination campaign, immediate and delayed vaccine-induced hypersensitivity reactions (HSRs) have been reported [5–8]. Although these reactions are rare adverse events, they need to be prevented, diagnosed, and managed in order to guarantee adherence to the vaccination campaign.

A careful allergy workup may be relevant for the stratification of patients at high risk of COVID-19 vaccine-induced HSR as well as for the diagnosis of HSR to the first dose. The estimate rate of mRNA COVID-19 vaccine-induced anaphylaxis was initially of 11.1 cases per million doses of the Pfizer/BioNTech, but subsequent reports revealed a lower rate of 4.7 and 2.5 cases with Pfizer/BioNTech and Moderna vaccines, respectively [9, 10]. Moreover, a recent meta-analysis showed case rate of anaphylaxis of 7.9 cases of all available COVID-19 vaccines, and no anaphylaxis-related fatalities were reported [11]. These data strongly suggest that even if severe reactions may occur after vaccination, these are very rare events and so far not fatal.

According to the literature, various components present in the currently available COVID-19 vaccines, including active and/or inactive ones, might be responsible for the development of HSR [12]. In this regard, polyethylene glycol (PEG) and polysorbates, excipients used to improve water solubility, were identified as potential allergens in COVID-19 vaccines, responsible for IgE-mediated reactions [1–4]. Since several drugs and nonmedical products (e.g., cosmetics) contain PEG and/or polysorbates, it has been postulated that a previous sensitization to these excipients might cause anaphylaxis during vaccination, even if the evidences supporting their role in HSR are still lacking [13–17]. Following first reports of COVID-19 vaccine-induced anaphylaxis [5–8], international and national scientific societies [18, 19] provided an algorithm for helping allergists to stratify patients at high risk of reactions and to perform *in vivo* skin tests for identifying PEG/polysorbates sensitization [20–22]. Assuming that patients who developed HSR were sensitized to vaccine components other than PEG/polysorbates, some medical centers tested the entire vaccine, getting however conflicting results. In fact, some [23, 24] but not all [25] clinical reports showed sensitization to components of the entire vaccine solution instead of drugs containing PEG/polysorbates.

Although HSR to the COVID-19 vaccines are rare and not life-threatening, it is still necessary to adopt all the diagnostic tools for the prevention and diagnosis of these reactions, useful to improve adherence to the vaccination campaign. Therefore, based on the clinical history and *in vivo* skin tests results, administration of the vaccine in graded doses regimen has been proposed as an alternative strategy to complete the vaccinal course [26]. In some cases, this approach has been successfully adopted [23, 27] using a protocol already proposed for other vaccines [28]. However, the immunological efficacy of COVID-19 vaccination using graded doses regimen has not been deeply investigated yet, and this issue is crucial for completing an efficient vaccinal course. Therefore, the aims of our study were to stratify in a large population the risk of developing HSR to currently available COVID-19 vaccines, to assess the role of *in vivo* skin tests for PEG/polysorbates in the diagnosis and prevention of COVID-19-induced HSR, and to identify safe and effective alternative strategies to complete the vaccinal course.

Methods

Patients

From February 2021 to September 2021, 1,640 subjects were screened for vaccinal eligibility, according to Banerji et al. [13] (Fig. 1). The study was part of a screening protocol for vaccine eligibility for COVID-19, organized by the health service of our region (Tuscany) to comply with published recommendations from AAIITO/SIAAIC societies [18]. Among them, 152 were enrolled at the Azienda Ospedaliera Universitaria Pisana, Pisa, Italy. Demographic and clinical characteristics of these patients were registered, including history of atopy, asthma, allergy to food and/or latex and/or venom of hymenoptera, and previous HSR to drugs and/or vaccines containing PEG/polysorbates. In those patients who experienced HSR to the first dose of COVID-19 vaccine, the reaction was classified on the basis of the time of onset (immediate or delayed) and severity (grades 1–5) [29].

In vivo Skin Test to PEG/Polysorbates

In all our cohorts, the *in vivo* skin tests (skin prick tests [SPT] and intradermal tests [IDT]) were performed using drugs and vaccines containing PEG/polysorbates, according to previous published protocols [13, 18, 22] with some modifications as reported in Table 1. Macrogol 3350 (pediatric Movicol without flavorings) and methylprednisolone acetate (Depo-Medrol) 40 mg/mL were used to evaluate sensitization to PEG 3350, while triamcinolone acetonide (Kenacort) 40 mg/mL, Optive lubricant eye drops, and Prevenar 13 were used to test sensitization to polysorbate 80. The hepatitis A vaccine Havrix was additionally tested as a source of polysorbate 20. Furthermore, methylprednisolone sodium succinate (Urbason) 40 mg/mL, containing neither PEG nor polysorbate 80, was used as additional control. SPT and IDT were evaluated after 15 min for immediate HSR and 24, 48, and 72 h or more for the delayed ones. The results of both SPT and IDT were com-

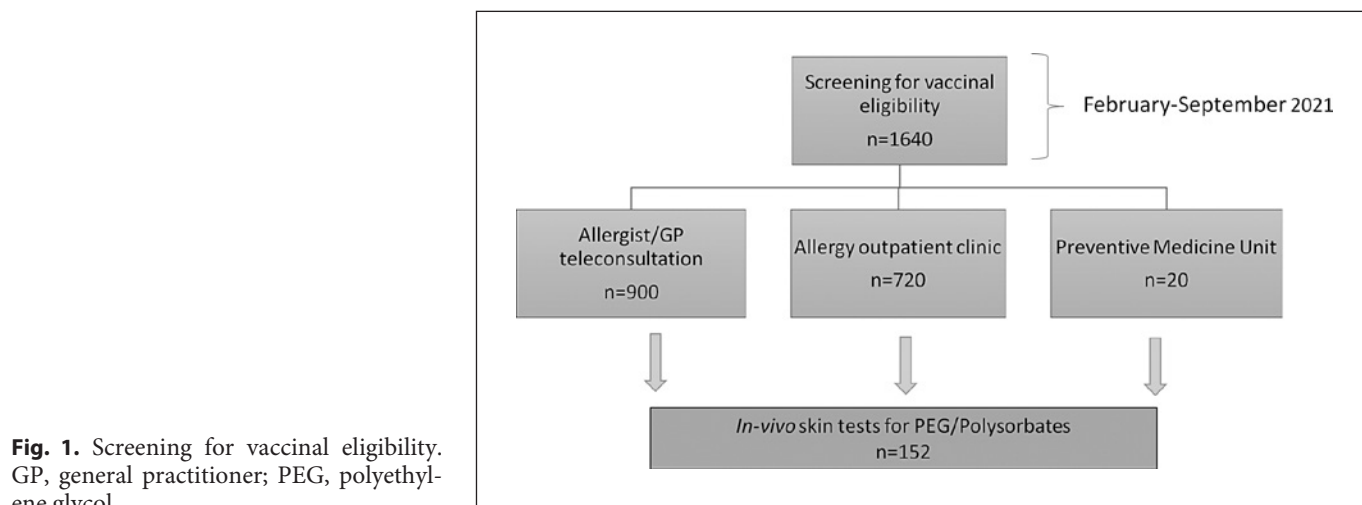


Fig. 1. Screening for vaccinal eligibility. GP, general practitioner; PEG, polyethylene glycol.

Table 1. Skin tests with drugs containing PEG 3350 and polysorbates

	PEG 3350		Control	Polysorbate 20	Polysorbate 80		Prevenar 13 (pneumococcal vaccine)
	Movicol (Macrogol), mg/mL	Depo-Medrol (MP acetate), mg/mL	Urbason (MP sodium succinate), mg/mL	Havrix (Hepatitis A vaccine)	Kenacort (TA), mg/mL	Optive	
Step 1 SPT	1.7	40	40	1:1	40	1:1	1:10
Step 2 SPT	17						
Step 3 SPT	170						
Step 4 IDT		0.04	0.04	1:100	0.4		1:100
Step 5 IDT		0.4	0.4	1:10	4		
Step 6 IDT		4	4		40		

IDT, intradermal tests; MP, methylprednisolone; SPT, skin prick tests; TA, triamcinolone acetonide.

pared with the results obtained with positive (histamine, Lofarma Allergeni, Milan, Italy) and negative (0.9% saline solution) controls, and an arbitrary score was assigned based on the size of the wheal (>3 mm). Informed written consent was obtained from each patient before performing the in vivo skin tests, according to the hospital internal protocol (Azienda Ospedaliera Universitaria Pisana, Pisa, Italy).

Different Strategies for COVID-19 Vaccination after in vivo Skin Tests

Based on the clinical history and the outcome of the in vivo skin tests, the patients were invited to be vaccinated according to the AAIITO/SIAAIC recommendations [18]. In order to know if they had successfully completed their vaccinal course, after the allergy workup a telephone interview was conducted. In the case of HSR, these patients were reevaluated in the allergy setting.

To improve the adherence to the COVID-19 vaccination campaign, we selected 18 consecutive subjects: 17 who developed an immediate HSR to the first dose (grade 1–3) with negative in vivo skin tests for PEG/polysorbates, and 1 at high risk of vaccine-induced HSR. The programmed dose of Pfizer/BioN-

Tech vaccine was administered using graded doses regimen as reported in Table 2. In order to reduce the risk of HSR, oral cetirizine (10 mg) was administered prior the vaccination, and the patients were observed 60 min after receiving the last dose of the vaccine.

Detection of Neutralizing Anti-Spike Antibodies

The neutralizing capacity of anti-spike antibodies was measured in 18 patients who received COVID-19 vaccines (Pfizer/BioNTech) in graded doses regimen. The serological analysis was performed 4 weeks after administration of the second vaccine dose, by using the kit SPIA (Spike Protein Inhibition Assay; DiaMetra, Perugia, Italy), according to the manufacturer's instructions. This assay is based on the competition between patient's antibodies and the peroxidase-conjugated ACE2 for the binding to viral receptor binding domain (RBD) coated on the solid phase. Sera samples were tested in duplicate at 1:15 dilution, and the inhibition value was calculated using the following formula: % inhibition = $(1 - [\text{absorbance sample}] / [\text{absorbance calibrator}]) \times 100$.

The results were compared to those obtained in the sera of 17 healthy subjects who received Pfizer/BioNTech COVID-19 vac-

Table 2. Graded doses regimen of Pfizer/BioNTech COVID-19 vaccine

Undiluted doses	Volume, mL	Time following previous dose, min
<i>Protocol 1 for patients with HSR to the first dose of COVID-19 vaccines</i>		
1	0.05	0
2	0.10	30
3	0.15	30
<i>Protocol 2 for patients at high risk of developing HSR to COVID-19 vaccine</i>		
1	0.05	0
2	0.25	30
COVID-19, coronavirus disease 2019; HSR, hypersensitivity reaction.		

Table 3. Demographic and clinical characteristics of patients

	Total, n = 152	First dose HSR, n = 43	High risk of HSR, n = 109	p value
Age, years, mean (range)	55 (20–93)	53.5 (23–89)	55.5 (20–93)	0.4611
Sex, M/F, n	19/133	4/39	15/94	0.4540
Atopy, n (%)	77 (51)	17 (39.5)	60 (55)	0.0849
Asthma, n (%)	42 (28)	12 (28)	30 (27.5)	0.9619
Food allergy, n (%)	27 (18)	7 (16)	20 (18)	0.7636
Hymenoptera venom allergy, n (%)	11 (7)	2 (5)	9 (8)	0.4396
Latex allergy, n (%)	15 (8)	5 (12)	10 (9)	0.6477
Urticaria/angioedema, n (%)	18 (12)	7 (16)	11 (10)	0.2876
AD and/or ACD, n (%)	27 (18)	8 (19)	19 (17)	0.8646
HSR to drugs and/or vaccines with PEG/polysorbates, n (%)	113 (74)	12 (28)	101 (93)	<0.00001
Anaphylaxis (grade 3–5)	65 (58)	5 (42)	60 (59)	0.2398
HSR to other vaccines, n (%)	20 (13)	2 (5)	18 (16.5)	0.0513
Mastocytosis or MCAS, n (%)	1 (0.6)	0 (0)	1 (1)	NA

ACD, allergic contact dermatitis; AD, atopic dermatitis; HSR, hypersensitivity reaction; n, number; MCAS, mast cells activation syndrome; NA, not applicable; PEG, polyethylene glycol.

cine in unfractionated dose. Neutralizing antibodies in both groups were then compared to those measured in 17 healthy subjects prior vaccination.

Statistical Analysis

Ages of the patients were expressed as mean of years (range) and compared using the Student *t* test. All the other variables were expressed as absolute number and percentage. The frequencies of atopy, asthma, and other clinical characteristics were compared using the χ^2 test for nonbinary comparisons. The percentage of neutralizing anti-spike antibodies in different groups were compared by the Kruskal-Wallis test. Data were analyzed and plotted using GraphPad Prism software (version 5.01; GraphPad Software Inc., San Diego, CA, USA). A *p* value <0.05 was considered statistically significant.

Results

Study Population

After screening for vaccinal eligibility in a large population, 152 subjects underwent allergy workup: 109 (72%) were at high risk of developing HSR to COVID-19 vaccines, according to the first published recommendation from AAIITO/SIAAIC societies [18] and 43 (28%) experienced a previous HSR to the first dose. Most of the subjects evaluated were females (87.5%) and to a lesser extent males (12.5%) with a mean age of 55 years (range 20–93); 77 (51%) were atopic, 42 (28%) asthmatics, and 74% reported a previous HSR to drugs or vaccines containing PEG/polysorbates. As reported in Table 3, analysis of the two subgroups evaluated revealed that less than 30% of patients in

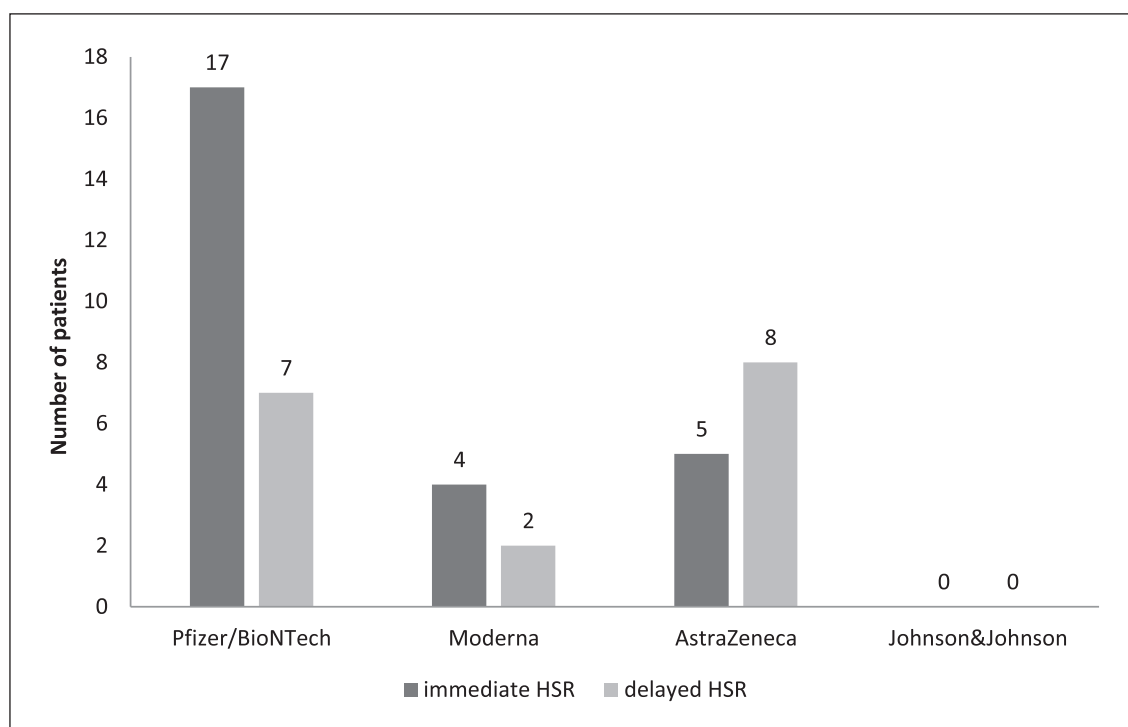


Fig. 2. Type of HSR to different COVID-19 vaccines according to the timing. COVID-19, coronavirus disease 2019; HSR, hypersensitivity reactions.

the group of subjects with a previous HSR to COVID-19 vaccines had a history of HSR to drugs or vaccine containing PEG/polysorbates. However, when we restricted this evaluation to only anaphylactic reactions (grade 3–5), this percentage was almost comparable to that of the subgroup at high risk of developing HSR to the COVID-19 vaccine. No differences in clinical and demographic parameters were detected between the two subgroups.

Characteristics of HSR to COVID-19 Vaccines

As reported in Figure 2, the most frequent HSR to the first dose of COVID-19 vaccines were observed after administration of Pfizer/BioNTech (56%), followed by AstraZeneca (30%) and Moderna (14%). Based on the time of onset, 60.5% were immediate and 39.5% were delayed reactions. Most of the reactions to Pfizer/BioNTech and Moderna were immediate (71% and 67%, respectively), while those to AstraZeneca were delayed (61.5%). Among the immediate ones, only 19% were severe (grade 4–5) and 38.5% classified as grade 3 (Table 4). A rescue medication with epinephrine was required in 4 out of the 5 patients who experienced a severe immediate HSR (grade 4–5) with resolution of the anaphylaxis within 1 h. No fatal events were reported.

Table 4. Grade of immediate COVID-19 vaccine-induced HSR

Grade	COVID-19 vaccine (n = 26)		
	Pfizer/BioNTech (n = 17), n (%)	Moderna (n = 4), n (%)	AstraZeneca (n = 5), n (%)
1	2 (12)	1 (25)	0 (0)
2	5 (29)	2 (50)	1 (20)
3	7 (41)	1 (25)	2 (40)
4	1 (6)	0 (0)	2 (40)
5	2 (12)	0 (0)	0 (0)

COVID-19, coronavirus disease 2019; HSR, hypersensitivity reaction; n, number.

Role of Skin Tests in the Diagnosis and Prevention of HSR to COVID-19 Vaccines

As reported in Figure 3, only 3% (5/152) of all the tested patients were positive to the in vivo skin tests, 3 at high risk of developing HSR to the first vaccine dose and 2 with a previous COVID-19 vaccine-induced HSR. Among the 3 patients at high risk of HSR, 2 successfully received the first dose of Pfizer/BioNTech vaccine.

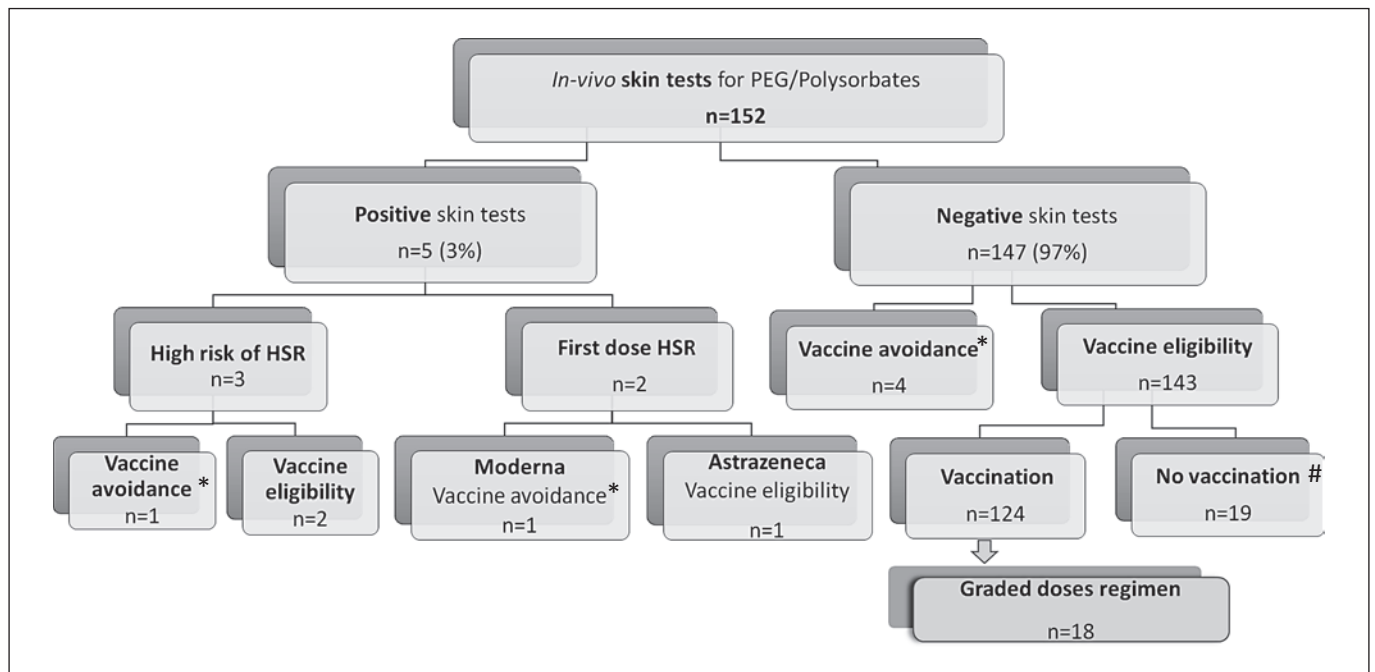


Fig. 3. In vivo skin test results and its impact on vaccinal eligibility. PEG, polyethylene glycol; HSR, hypersensitivity reaction. *Vaccine avoidance: the vaccination was not recommended by an allergist, according to the results of in vivo skin tests [18]. #No vaccination: the vaccination was refused by the patient even if he was eligible for the vaccination.

The 2 patients with a previous HSR to the first dose, one to Moderna (immediate HSR) and the other one to AstraZeneca (delayed-HSR), resulted positive to Kenacort (polysorbates containing drug), but no sensitization to Macrogol (PEG 3350) has been detected. Therefore, who developed an immediate HSR to Moderna vaccine was not eligible for the second dose of COVID-19 vaccine containing PEG/polysorbates, while who developed the HSR to AstraZeneca was eligible for vaccination and successfully received the second dose of Pfizer/BioNTech vaccine.

In most of the patients tested (97%; 147/152), no sensitization to PEG/polysorbates has been detected by in vivo skin tests, and they were advised to receive the COVID-19 vaccine, according to the recommendations [18]. At the reevaluation, 84% (124/143) completed the vaccination course, 3% (4/124) with a mild-moderate immediate HSR (grades 1–3), and 1.6% (2/124) with a severe immediate HSR (grade 4), none requiring epinephrine injection.

In order to improve the adherence to the vaccinal campaign, we selected 18 out of the 147 patients, resulted negative to the skin tests for receiving the programmed dose using graded doses of Pfizer/BioNTech vaccine, 17 with

a previous immediate HSR to the first dose, and one at high risk of reaction. The graded doses were well tolerated in most of the patients; only one developed an immediate HSR (grade 2), less severe than the previous one (grade 3), resolved after medical intervention with injective corticosteroids.

Immunological Response in Graded Doses of COVID-19 Vaccine

In order to evaluate the immunological efficacy of the COVID-19 vaccination with Pfizer/BioNTech vaccine using graded doses regimen, we evaluated neutralizing RBD/ACE2-binding antibodies in the sera of these patients 4 weeks after completing the vaccinal course. As reported in Figure 4, neutralizing antibodies were produced in this group at the same level as those produced in the group that received the unfractionated dose, indicating that graded doses regimen of Pfizer/BioNTech COVID-19 vaccine does not impair the production of protective antibodies. The neutralizing antibodies in both groups (unfractionated and graded doses) were significantly higher than those detected in the healthy subjects prior vaccination ($p < 0.0001$) (Fig. 4).

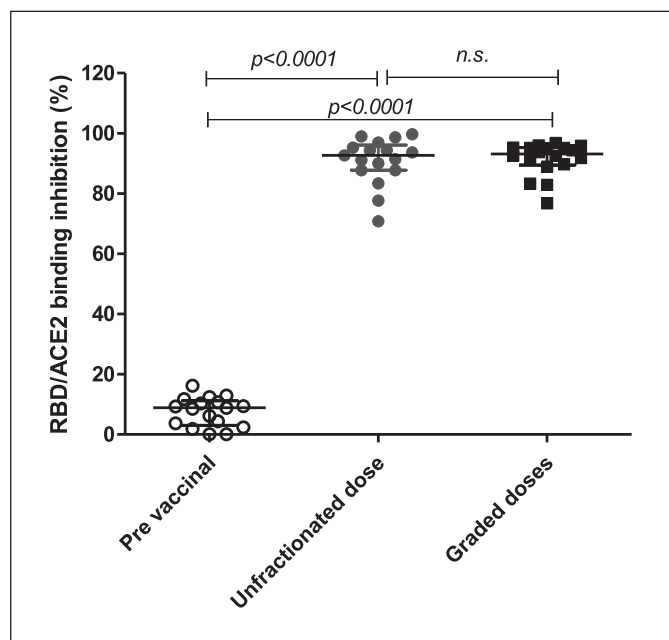


Fig. 4. Neutralizing anti-spike antibodies following graded doses of Pfizer/BioNTech COVID-19 vaccine. A p value <0.05 was considered statistically significant. RBD, receptor binding domain; ACE2, angiotensin-converting enzyme 2; n.s., not significant.

Discussion

Since the beginning of COVID-19 vaccination campaign, the main goal of allergists was to prevent COVID-19 vaccine-induced HSR and, in the case of reactions, to adopt an allergy workup for the diagnosis and the management of them. In line with other allergy centers [17, 26, 30–32], and according to the national and international recommendations [18, 19], we performed, when indicated, risk stratification of HSR to COVID-19 vaccines and allergy workup, including in vivo skin tests for identifying sensitization to PEG/polysorbates [13, 18, 22].

Our cohort included 72% of patients at high risk of HSR to COVID-19 vaccine and 28% with previous HSR to the first dose. As reported in other centers [8, 32], the majority of subjects requiring an allergy workup were females, even though no other differences in clinical characteristics were identified between males and females (data not shown). The atopic status and a previous diagnosis of asthma were not able to discriminate between patients at high risk of HSR versus those who developed HSR to the first dose. Although a previous HSR to drugs or vaccines containing PEG/polysorbates was identified as a high risk factor for developing a COVID-19 vaccine-

induced HSR, in our cohort this parameter was not predictive of reaction and did not affect either the detection of sensitization of PEG/polysorbates using skin tests or the subsequent tolerance of COVID-19 vaccine in subjects with previous HSR. In fact, most of the patients with HSR to the first dose and/or previous HSR to drugs or vaccines containing PEG/polysorbates were able to receive safely the COVID-19 vaccine. These data were confirmed by the most recent AAIITO/SIAAIC recommendations (available from April 2022) [33] that include in the group of subjects at “high risk” of HSR to COVID-19 vaccine only those with previous HSR to injectable drugs containing PEG, to echocardiographic contrast agents, or to laxatives, or bowel preps for colonoscopy, both containing PEG as active components. On the contrary, the subjects reporting a previous HSR to oral drugs containing PEG/polysorbates are now considered at “low risk” to develop HSR to COVID-19 vaccine [33].

In our experience, most of the HSR to the first dose of COVID-19 vaccines were immediate and not anaphylactic (grade 1–2), with a prevalence of erythema and/or urticaria as clinical manifestations. In line with previous reports [17, 26, 30–32], only 5% of the patients with HSR to the first dose resulted positive to skin tests to drugs and/or vaccine containing PEG/polysorbates. However, even if it was not possible to identify a sensitization to PEG/polysorbates, these excipients might still be involved in COVID-19 vaccine-induced HSR through other mechanisms such as non-IgE-mediated or nonimmunological ones. Moreover, we can suggest that the active components of the vaccines, rather than excipients, may be responsible for vaccine-induced HSR, and the in vivo skin tests used in the allergy workup are not able to identify it.

In our cohort, the in vivo skin tests for identifying sensitization to PEG/polysorbates revealed an unexpected low rate of positive results despite a previous HSR to drugs and/or vaccines containing PEG/polysorbates. Under this respect, it should be taken into account that the molecular weight (MW) of PEG contained in COVID-19 vaccines (Pfizer/BioNTech and Moderna) is 2,000, not the same MW of PEG commonly used in other drugs. Therefore, these differences might in part explain the negative skin test results obtained in our and in other studies. Thus, the level of cross-reactivity among PEG polymers with different MW needs to be further investigated. Moreover, when skin tests to drugs and vaccines containing PEG/polysorbates are negative, we should perform skin tests using PEGylated liposomes [24]. In fact, skin testing to native PEG may provide negative results, while their sensitivity may be improved by testing

PEGylated liposomes, which more closely resemble the form of PEG contained in COVID-19 vaccine [24]. According to our results, we can assume that skin tests using drugs and vaccines containing PEG/polysorbates are not optimal for the diagnosis of HSR to COVID-19 vaccines and their usefulness and validity need to be reconsidered. The use of culprit vaccine for in vivo skin tests may overcome some of these limitations, but positive results by this approach were less frequent than expected as described in some reports [25]. Thus, other diagnostic tools for identifying PEG/polysorbates sensitization [26, 32] are required, including detection of specific IgE and/or basophil activation test.

Despite the limits of the currently available diagnostic tools, the main goal for allergists remains the identification of safe and effective alternative strategies useful to complete the vaccinal course. According to national and international recommendations [18], a desensitization protocol should be considered in selected patients with a previous immediate HSR to COVID-19 vaccines, with no evidence of sensitization to PEG/polysorbates. However, the stability, the safety, and the immunogenicity of the vaccine diluted, as required by desensitization protocols [18], have not been deeply investigated yet [13]. Therefore, this vaccinal strategy has some limitations that need to be overcome. Thus, we decided to administer Pfizer/BioNTech COVID-19 vaccine not diluted by using graded doses regimen in order not to impair the stability of the nanoparticles. According to our results, this approach was useful to complete the vaccinal course in subjects at high risk of HSR to the first dose and/or after a previous HSR. In fact, most of them did not develop any HSR during the vaccine administration, and in only one case, the HSR observed was less severe than the previous one. Our goal was also to complete the vaccinal course by means of an alternative strategy effective in inducing a specific immunological response. Our data confirmed that after 4 weeks from Pfizer/BioNTech COVID-19 vaccine in graded doses regimen, these patients developed protective neutralizing anti-spike antibodies. This is the first report demonstrating that graded doses regimen of COVID-19 vaccination is able to induce an efficient immunological response comparable to unfractionated doses. In line with our experience, few other Allergy centers administered safely COVID-19 vaccines by using the same approach [23, 27, 34]. In only few clinical reports, the anti-spike antibodies were measured after receiving the COVID-19 vaccine in graded doses regimen, but their neutralizing capacity was not evaluated [27, 34].

In conclusion, although COVID-19-induced HSRs are very rare adverse events, the fearfulness of developing these reactions can cause loss of adherence to the vaccinal campaign. Therefore, the allergy workup is useful to stratify the risk of developing HSR to COVID-19 vaccines and to identify safe and effective alternative strategies to complete the vaccinal course. However, the usefulness of the skin tests for PEG/polysorbates seems limited in the diagnosis of HSR to COVID-19 vaccines and other diagnostic tools are required. Graded doses of Pfizer/BioNTech COVID-19 vaccine has resulted a safe and effective alternative strategy to complete successfully the vaccinal course.

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The clinical protocol was approved by the Ethical Committee of the Pisa University Hospital (approval No. 17522). Informed written consent was obtained from all the participants.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Fiorella Petrelli, Daiana Giannini, Celestino Pucci, Isabella Del Corso, Valeria Rocchi, Maria Pia Dolcher, Giulio Pieve, Federico Pratesi, Paola Migliorini, and Ilaria Puxeddu made substantial contributions to conception and design, acquisition of data, and interpretation of data; reviewed it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work related to its accuracy or integrity; Fiorella Petrelli, Daiana Giannini, and Ilaria Puxeddu drafted the article.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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